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MS MANON ANTOINET ZWAKENBERG (Orcid ID : 0000-0002-6825-7932)

DR JAN WEDMAN (Orcid ID : 0000-0001-6448-134X)

PROFESSOR BERNARD F.A.M. VAN DER LAAN (Orcid ID : 0000-0002-5016-2871)

DR GYORGY B HALMOS (Orcid ID : 0000-0003-2460-2260)

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## **Detection of high-grade dysplasia, carcinoma in situ and squamous cell carcinoma in the upper aerodigestive tract: recommendations for optimal use and interpretation of Narrow Band Imaging**

Manon A. Zwakenberg, MD<sup>1</sup>; Frederik G. Dikkers<sup>2</sup>, MD, PhD; Jan Wedman<sup>1</sup>, MD; Bernard F.A.M. van der Laan<sup>1</sup>, MD, PhD; Gyorgy B. Halmos<sup>1</sup>, MD, PhD; Boudewijn E. C. Plaat<sup>1</sup>, MD, PhD

<sup>1</sup>Department of Otorhinolaryngology/Head and Neck surgery, University of Groningen, University Medical Center Groningen, the Netherlands

<sup>2</sup>Department of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, the Netherlands

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Corresponding author: Manon A. Zwakenberg, MD, Department of Otorhinolaryngology/Head and Neck Surgery, University of Groningen, University Medical Center Groningen, P.O. Box 30001, 9700 RB Groningen, the Netherlands. Telephone number +31503612540, fax number +31503611698. E-mail: m.a.zwakenberg@umcg.nl

## **Abstract**

**Objectives:** The primary goal was to study the diagnostic potential of Narrow Band Imaging (NBI), the secondary was to evaluate the most common mistakes when using and interpreting NBI.

**Design:** Retrospective study.

**Setting:** University Medical Center Groningen, tertiary referral hospital, the Netherlands.

**Participants:** Three hundred seventy patients who underwent rigid endoscopy of the upper aerodigestive tract. Two observers assessed all lesions. Twelve observers assessed a selection of 100 lesions. All observers were provided with both WLI and NBI.

**Main outcome measures:** Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and reasons for insufficient photo quality.

**Results:** When using NBI, the sensitivity, specificity, PPV, NPV and accuracy for detecting invasive carcinoma, carcinoma in situ or high-grade dysplasia were 92%, 68%, 61%, 94% and 77%, respectively. In multiple observer analysis, values were 76%, 58%, 53%, 83% and 65% with the evaluation strictly based on type V patterns of Ni's classification, versus 83%, 68%, 64%, 85% and 74% when evaluation was also based on lesion-specific clinical characteristics. Lesions that caused

misinterpretations were: leukoplakia, papillomas and mucosal lesions after irradiation. In total, 185 photos were assessed to be of suboptimal quality due to blurring (36%), bleeding (6%), insufficient zooming (15%) and/or insufficient lighting (17%).

**Conclusion:** NBI is a relatively reliable screening method for detecting malignancy. Evaluation based on Ni's classification alone is not sufficient. To optimise NBI photo quality, we recommend sufficient zooming and prevention of bleeding, blurring and inadequate lighting.

## Introduction

Narrow Band Imaging (NBI) enhances visualisation of superficial mucosal vascular patterns and it identifies intraepithelial papillary capillary loops (IPCLs), which are important determinants for the histopathological diagnosis<sup>1,2</sup>. NBI is superior to conventional white light imaging (WLI), since it improves the detection rate of small superficial malignant lesions<sup>1,3-11</sup>. The classification introduced by Ni (varying from I to Vabc) is commonly used to categorise vascular patterns of the larynx<sup>1</sup>. Type V patterns are considered to be significant predictors of invasive cancer. Recently, a systematic review of the diagnostic performance of NBI has appeared; a meta-analysis of six studies revealed a pooled sensitivity of 94% and specificity of 89% of evaluations with NBI, compared to values of 81% and 92%, respectively, from white light endoscopy<sup>12</sup>. The reported sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in studies that were not included in this meta-analysis were 88.9-100%, 84.6-97.5%, 79-91.6% and 91.7-100% respectively<sup>1,4,5,7,8,10</sup>. Besides these promising results, problems in the interpretation have also been reported, especially in irradiated mucosa and in the differentiation between papilloma and carcinoma<sup>4,9,13-17</sup>. Little is known about poor photo quality due to incorrect NBI usage. The aim of this study was to evaluate the diagnostic potential of NBI and to establish recommendations on how to use and interpret NBI adequately.

## Materials and Methods

### *Ethical considerations*

This study was approved by the institutional ethical review board of the University of Groningen.

### *Setting and lesions*

Between August 2012 and December 2014, 370 endoscopies of the upper aerodigestive tract were performed using both conventional WLI and NBI at the department of otorhinolaryngology of the University Medical Center Groningen, the Netherlands. Endoscopic procedures were performed according to standard protocol under general anaesthesia, using an Olympus HD camera head with a 0°, 5.4-mm telescope and Evis Exera CLV-180 light source (Olympus BV, Zoeterwoude, the Netherlands)<sup>18</sup>. Patient data and images were stored in the electronic patient records and analysed retrospectively.

### *Observers*

Two of the authors (MZ, MD, PhD student; BP, experienced head-and-neck oncologist) independently assessed all 370 lesions based on photo quality. The photo quality was considered insufficient if one observer assessed a photo as 'of suboptimal quality'. Half of all lesions (n=185) were assessed as suboptimal: 143 lesions by both observers, 42 lesions by only one observer. Exclusion criteria were: unavailability of either WLI or NBI photos, unknown histopathological diagnosis, or localisation outside the larynx or pharynx (n=7). The remaining 178 lesions were evaluated by both observers independently. The diagnosis was primarily based on WLI, followed by defining the Ni classification in the corresponding NBI photo. In a case of disagreement, the image was discussed until consensus was reached. All type V patterns were considered to be suspect for malignancy. A selection of one hundred lesions was also evaluated by twelve additional observers. This representative selection contained 50 benign lesions, 25 dysplasias and 25 SCC's. The observer group comprised three head-and-neck oncologists, one laryngologist and eight ENT trainees with one

to five years' training. Observers were asked to discriminate between benign and malignant, but without maintaining strict criteria. First, the white light image was assessed, followed by NBI of the corresponding lesion. The Ni type of every lesion was subsequently assessed. Histopathological diagnoses were used as the gold standard. High-grade dysplasia, carcinoma in situ and invasive carcinoma were considered as a positive outcome. Sensitivity, specificity, PPV, NPV and accuracy were calculated. In our multiple-observer analysis, the final diagnosis was based on the opinion of the majority of the group ( $\geq 7$  observers).

### *Statistical analysis*

Calculations were performed using SPSS version 22.0 using (IBM Corp., Armonk, NY, USA). The database was saved in Excel 2007 (Microsoft Corp., Redmond, WA). Figures were composed with Adobe illustrator CS6 (Adobe Systems Software Ireland Ltd).

## **Results**

Analysis by two observers: 370 lesions

One hundred and eighty-five photos were judged as suboptimal. The four most common mistakes included blurring, insufficient zooming, insufficient lighting and underlying mucosa being masked by blood (Table 1). Figure A in our supplementary data shows examples of incorrect use of Narrow Band Imaging leading to insufficient photo quality. Reasons causing blurring concerned a fogged lens, blood or mucus in front of the camera, inadequate focusing, non-perpendicular approach or camera movement. Obscuring blood caused insufficient photo quality in 21 lesions, of which 15 (71%) concerned SCC.

The relationship between Ni's IPCL classification and the histopathological diagnosis is presented in Table 2. Type I and II vascular patterns were present in benign lesions only. Mild to moderate dysplasia showed type III or type IV patterns (10/12). Irradiated mucosa showed type IV or V IPCLs, even when no recurrence was detected (25/26). Ninety-six per cent of all invasive carcinomas (45/47)

presented with type V patterns. The false negative rate of NBI was 7.9% (5/63), i.e. malignant lesions with a type I-IV pattern. Lesions concerned one recurrent SCC with a type IV pattern (after radiotherapy), one SCC with a type III pattern and three high-grade dysplasias with type III patterns. The false positive rate was 38.9% (37/95), i.e. benign lesions with a type V pattern. False positive type V patterns were seen in all papillomas (n=16), post radiotherapy atypia (n=17), mild to moderate dysplasia (n=2), verrucous hyperplasia (n=1) and amyloidosis (n=1). Examples of false negative and positive vascular patterns are presented in Figure 1. An overview of the achieved sensitivity, specificity, PPV, NPV and accuracy for diagnosing high-grade dysplasia, carcinoma in situ or invasive carcinoma for both WLI and NBI is given in table 3. The diagnostic potential of WLI was evaluated based on strict criteria (white, red, exophytic or ulcerative lesions) and based on clinical evaluation. For NBI, three subgroup analyses were performed: firstly, type Va, Vb and Vc were all considered to be suspect for malignancy; secondly, only type Vb and Vc were considered suspect; thirdly, evaluation of the same 100 lesions as in our multiple-observer analysis was performed.

Excluding all papillomas, the sensitivity becomes 92%, specificity 88%, PPV 73%, NPV 94% and the accuracy 84%. Of the 35 patients who were previously irradiated, 8 presented with recurrent or residual tumours that were all correctly identified. The remaining 27 lesions after radiotherapy were considered sequelae (n=26); one was a benign vocal fold polyp. Excluding all previously irradiated patients and papillomas, the sensitivity, specificity, PPV, NPV and accuracy were 93%, 94%, 93%, 94% and 94% respectively. Values for evaluation with WLI alone in this subgroup analysis were 93%, 65%, 68%, 92% and 77% respectively.

Analysis by twelve observers, 100 lesions

Twenty patients previously received (chemo)radiation, of whom three were diagnosed with SCC and two with high-grade dysplasia. Sensitivity, specificity, PPV, NPV and accuracy of evaluation with WLI and NBI are presented in table 3. For NBI, separate columns show the values for an evaluation solely based on clinical evaluation versus an evaluation strictly based on Ni type V. By adding NBI,

the sensitivity and NPV increased, although both specificity and PPV decreased. When evaluation was strictly based on type Vabc patterns, 10 false negative assessments and 25 false positive assessments were found. All lesions in our study that were misjudged by more than 50% of all observers are shown in figure 2. In all false negative cases, leukoplakia was present, whether or not accompanied by type IV or V patterns. Lesions were misinterpreted as hyperkeratosis or mild dysplasia. Of the false positive assessments, 71% (10/14) concerned previously irradiated patients. Only 33% (5/15) of the benign mucosal radiotherapy associated changes were accurately assessed as negative. No malignancies after previous radiotherapy were missed.

## Discussion

### Key findings

Our study demonstrates that NBI is a reliable tool for detecting high-grade dysplasia, carcinoma in situ and invasive carcinoma. Specificity of NBI is influenced by the heterogeneity of the study cohort and by the established criteria for diagnosing malignancies, e.g., diagnosis strictly based on Ni's classification versus also taking into account other lesion specific characteristics. Especially in papillomas and irradiated mucosa, the number of false positive assessments when using NBI is higher; in these cases Ni's classification alone is not sufficient. Leukoplakia can cause false negative assessments. NBI also has a learning curve: The quality of the photos and their interpretation will increase over time.

### Ni's classification

Our study confirms the association between the IPCL-classification and histopathological diagnosis. Type V patterns have a high sensitivity (92%) and NPV (94%) for detecting malignancy, which is consistent with results published in several studies<sup>1,5,11,17</sup>. The sensitivity was lower in our multiple observer analysis: 76% with evaluation strictly based on type V patterns versus 83% taking both lesion-specific and vascular pattern characteristics into account. This might be explained by the



limited experience of the observers with NBI at the time of the study; besides, consensus-based evaluation is presumably more reliable. However, consensus-based evaluation is not common in daily clinical practice. In previous studies, evaluation was often based on multiple observer opinions<sup>4,9,11</sup> or it was not made clear whether the analysis was performed by one or more observers<sup>1,5,13,14</sup>. Unfortunately, the diagnostic potential of NBI based on clinical evaluation in our two-observer group was not evaluated. We are convinced that the sensitivity of NBI would increase and would at least equal the sensitivity of evaluation using WLI alone.

The specificity of NBI in our study was lower than expected. The specificity of NBI was, however, similar in the 2-observer and the multiple-observer group, especially when the same 100 lesions were evaluated (59% versus 58%)<sup>4,5,9,11,19</sup>. The specificity increased greatly when only type Vb and Vc were considered to be suspect for malignancy; however, this increase in specificity was accompanied by an unacceptable decrease in sensitivity. A remarkable increase in the diagnostic potential of NBI was observed when evaluation was not strictly based on the Ni classification. Apparently, observers intuitively took other important clinical characteristics into account. Another explanation for the lower specificity in the present study could be the strict boundary we employed between positive and negative outcome (between high-grade and moderate dysplasia). Kraft et al.<sup>11</sup> considered moderate dysplasia as positive outcome and Bertino et al.<sup>5</sup>, the authors of the only study with a comparably large, heterogeneous study sample, did not, unfortunately, clearly define the boundaries between benign lesions and malignancy. As described by Sun et al., it is difficult to compare the results of all NBI studies, because of their observational nature, the corresponding heterogeneity, and lack of standardised cut-off values<sup>12</sup>.

#### Common misinterpretations

Leukoplakia, papillomas and lesions in irradiated mucosa were prone to misinterpretation. Type III patterns are usually benign lesions, but the white layer could cover a malignant lesion. In figure 3, three type III lesions are presented, with histopathological diagnoses ranging from hyperplasia to high-grade dysplasia. The difference between benign and malignant type III lesions is a thin,

transparent white layer with a symmetrical border in benign lesions versus a more irregular leukoplakia regarding both border and thickness when the epithelium becomes dysplastic, as described by Arens et al<sup>21</sup>.

In the present study, all 16 papillomas were classified as type V lesions, similar to the vascular changes seen in carcinomas; this is concordant with previous studies<sup>13-15</sup>. Specificity, PPV and accuracy increased dramatically when all cases with papilloma were excluded from the study. It can be concluded that type V patterns alone are insufficient to differentiate between papilloma and SCC. In our multiple-observer analysis, however, 12 out of 16 papillomas were correctly identified. To adequately distinguish between cancer and papillomas, IPCLs must be evaluated, but several typical clinical characteristics must also be taken into account<sup>14</sup>. Unlike in malignant lesions, IPCLs in papillomas are often symmetrical<sup>20,21</sup>. Papillomas present with a typical shimmering, pale, wart-like appearance, with a central vessel in each papilla, often on multiple locations in one patient<sup>14,15,17,21,22</sup>. Leukoplakia, ulceration and a rough surface are uncommon in papillomas<sup>14,15,17,22</sup>.

Previous studies showed that NBI can accurately distinguish between post-radiation changes and recurrent/residual tumours<sup>7,9,16</sup>. In our study, type IV or V patterns were present in 96% of the patients with benign post-radiation changes, which often led to false positive assessments. Possibly the term telangiectasia is more appropriate for the vessels observed in irradiated mucosa, but these are not incorporated in Ni's classification<sup>1</sup>. Arens et al. did incorporate 'ectasia' in their descriptive classification<sup>20</sup>. (Chemo)Radiation leads to mucosal changes such as inflammation, hypervascularisation and oedema. Therefore, and due to the frequent presence of viscous mucous, detection of subtle vessel-pattern changes in irradiated cases is difficult<sup>4</sup>. There is a need for a separate classification that is suitable for irradiated patients. Lin and Piazza used well-demarcated, brownish areas with type V patterns as the criterion to detect malignancy<sup>9,16</sup>. This well-demarcated brown area could be another important indicator to distinguish between radiotherapy effects and

malignancy. One should focus on regularly distributed, low density IPCLs with poorly defined margins (which are not suspect for malignancy) versus irregular vascular patterns in a clearly demarcated brown area with an uneven surface (suspect for malignancy). Zabrodsky et al. suggested taking other tumour-characterising factors into account, such as ulceration, necrosis, and pronounced feeding vessels, but also patients' physical complaints<sup>4</sup>. Prospective studies on the utility of NBI in irradiated patients are currently running in our clinic.

#### How to use NBI correctly

In this retrospective study, half of all photos were assessed as of insufficient quality. This study gave us the opportunity to evaluate the 'mistakes' each oncologist/laryngologist will encounter when initially using NBI. As described earlier by Ishihara et al., a six-month learning period can be expected for evaluation of NBI images<sup>23</sup>. This learning curve most likely also applies to using NBI, since evaluation with NBI differs from inspection with WLI. For adequate use of NBI, we recommend careful near-contact inspection. Bleeding and blurring must be prevented. Mucosal damage due to coarse intubation must be precluded (consider using supraglottic High-Frequency Jet Ventilation). Damaging of the mucosa by suction must be minimised, since this can cause small mucosal suction spots which resemble type IV or V vascular patterns. Adequate zooming and focusing is crucial. A fogged lens can be prevented by using anti-fog solution or dipping the telescope in clean hot water. Blood or mucus must be removed and the camera head must be held still while taking pictures; using videos is even better, as it provides the opportunity to evaluate high-definition moving images. An overview photo works for WLI, but is not informative when using NBI.

#### Drawbacks and recommendations

We were strict in deciding whether or not image quality was sufficient. Therefore the number of 'mistakes' may be overestimated. In future research, the recently published dichotomous vascular pattern classification of the European Laryngological Society might lead to more reliable

identification of high-risk lesions<sup>20</sup>. Clear guidelines on the interpretation of NBI are needed. To achieve the most reliable diagnostic tool, these guidelines should also define the combination of vascular patterns with lesion-specific characteristics.

## Conclusion

NBI is a relatively reliable screening method for detecting high-grade dysplasia, carcinoma in situ or invasive carcinoma. Difficulties in the interpretation are encountered for papillomas, leukoplakia and in irradiated mucosa. Evaluation solely based on Ni's classification is not sufficient: lesion specific clinical features must also be taken into account. To use NBI adequately, we recommend sufficient zooming and prevention of bleeding, blurring and inadequate lighting.

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**Table 1. Reasons for insufficient Narrow Band Imaging photo quality**

	Pitfall	No. of patients	%
Single 'mistake'	Blurring	56	15
	Insufficient zooming	11	3
	Too dark	22	6
	Blood	8	2
	Overexposure	2	0.5
Double 'mistake'	Insufficient zooming and blurring	34	9
	Too dark and blurring	19	5
	Blood and blurring	11	3
	Overexposure and blurring	8	2
	Too dark and insufficient zooming	5	1
	Blood and too dark	2	0.5
	Overexposure and insufficient zooming	1	0.3
Triple 'mistake'	Too dark, blurring and insufficient zooming	6	2
	Total	185	50
Totals	Blurring	134	36
	Insufficient zooming	57	15
	Too dark	52	14
	Blood	21	6
	Overexposure	11	3

No. = number, % = percentage of the total group of 370 lesions. Percentages below 1 were rounded to 1 decimal place, percentages above 1 were rounded to whole numbers.



**Table 2. Relation between Narrow Band Imaging (Ni's classification) and histopathological diagnosis**

Histopathological diagnosis	Ni type					Total		
	I	II	III	IV	V			
					a	b	c	
Without mucosal pathology (×)	5	2	-	-	-			7
Vocal fold polyp	1	2	1	-	-			4
Vocal fold nodule	9	-	-	-	-			9
Cyst (*)	1	9	-	-	-			10
Reinke's oedema	-	-	3(»)	-	-			3
Reactive changes: hyperplasia, fibrosis, hyper-/parakeratosis	-	8	12	4	1(#)			25
Papilloma	-	-	-	-	7	7	2	16
Mild to moderate dysplasia	-	-	8	2	1	1		12
High-grade dysplasia/ carcinoma in situ	-	-	3	-	8	4	1	16
Squamous cell carcinoma	-	-	1	1	19	19	6	46
Previous (chemo) radiation, without recurrence	-	1	-	8	5	6	6	26
Remaining group		2(^)			1(~)	1(=)		4
Total	16	24	28	15	95			178

(×) Vocal fold atrophy, unilateral vocal cord fixation, not further specified lesion

(\*) Including two oncocytic papillary cystadenomas

(») All Reinke's oedemas presented with combined type II and III patterns

(#) Verrucous hyperplasia with parakeratosis (type Va IPCL pattern)

(^) Hamartoma, PEComa

(~) Amyloidosis,

(=) Adenoid cystic carcinoma

Table 3. Overview of diagnostic accuracies for detecting high-grade dysplasia, carcinoma in situ or invasive carcinoma with white light imaging (WLI) versus Narrow Band Imaging (NBI).

Diagnosis based on:	2 observers (178 lesions)					12 observers*** (100 lesions)			
	WLI	WLI	NBI	NBI	NBI **	WLI	NBI	NBI	NBI
	Clinical evaluation	Strict criteria*	Type Vabc suspect	Type Vbc suspect	Type Vabc suspect	Clinical evaluation	Clinical evaluation	Type Vabc suspect	Type Vbc suspect
Sens. (%)	94	95	92	49	93	73	83	76	49
Spec. (%)	48	31	68	82	59	81	68	58	88
PPV (%)	50	44	61	60	62	71	64	53	63
NPV (%)	93	92	94	75	92	81	85	83	76
Acc. (%)	65	54	77	70	73	77	74	65	72

Sens. = sensitivity, Spec. = specificity, PPV = positive predictive value, NPV = negative predictive value, Acc. = Accuracy

\* Strict criteria comprised white, red, exophytic or ulcerative lesions.

\*\* Subgroup analysis of the same 100 lesions as in the multiple (12) observer analysis.

\*\*\* Opinion of the majority of the group; i.e. the diagnosis of  $\geq 7$  observers.

## Legends

**Figure 1. Examples of lesions in which intra-epithelial papillary capillary loop patterns (IPCLs) do not correspond to the histopathological diagnosis**

A. Type III, high-grade dysplasia; B. Type II and III, high-grade dysplasia; C. Type III, high-grade dysplasia; D. Type IV (posterior pharyngeal wall in a previously irradiated patient), squamous cell carcinoma; E. Type Vb, papilloma; F. Type Vc, post radiotherapy atypia with active inflammation and presence of fungi; G. Type Va, moderate dysplasia; H. Type Vb (and III), moderate dysplasia; I: Type Va, laryngeal amyloidosis. Panel A-D correspond with false negative patterns; panel E-I with false positive patterns.

**Figure 2. All lesions which were misjudged by more than 50% of the observers in our study: false negative (A-C) and false positive (D-N) assessments.**

A. Type III, IV and Va, high-grade dysplasia; B. Type III and Vb, squamous cell carcinoma (SCC); C. Type Vb, *High-grade dysplasia*; D. Type Va, *chronic ulcerative inflammation (irradiated patient)*; E. Type III and IV, *lichenoid inflammation*; F. Type Vb, *papilloma (after multiple resections)*; G. Type Va, *laryngeal oedema (irradiated patient)*; H. Type Vb, *mild dysplasia, radiotherapy atypia*; I. Type Va, *ulcerative inflammation, candida infection (irradiated patient)*; J. Type Vc, *mild dysplasia (irradiated patient)*; K. Type Vb, *hyperplasia (irradiated patient)*; L. Type Va, *radiotherapy atypia*; M. Type Va, *moderate dysplasia (irradiated patient)*; N. Type Va, *post radiotherapy atypia*; O. Type IV, *hyperplasia and inflammation*.

**Figure 3. Three lesions presenting with leukoplakia/type III vascular patterns (Ni's classification), corresponding to three different histopathological diagnoses ranging from benign to malignant.**

A. left vocal fold: polyp, right vocal fold: secondary lesion with convolute; B. mild dysplasia; C. high-grade dysplasia.







